Xenotransplantation: an insight

Sumitra Panigrahi¹, Krutanjali Swain², Abhilash Routray¹, Subha Ganguly³*

¹Department of Veterinary Public Health and Epidemiology, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana, ²Department of Veterinary Parasitology, College of Veterinary Science and Animal Husbandry, Chattisgarh Kamedhenu Vishwavidyalaya, Raipur, Chattisgarh, India
³Department of Veterinary Microbiology, Arawali Veterinary College (Affiliated to Rajasthan University of Veterinary and Animal Sciences, Bikaner), Bajor, Sikar, Rajasthan, India

*For correspondence
Dr. Subha Ganguly,
Department of Veterinary Microbiology, Arawali Veterinary College, Bajor, Sikar, Rajasthan, India.
Email: ganguly38@gmail.com

Received: 11 November 2017
Accepted: 21 November 2017

ABSTRACT

Xenotransplantation is defined as the transplantation of organs, tissues or cells from one animal species into another. In human, It is defined as any procedure that involves the transplantation, implantation or infusion into a human recipient of either live cells, tissues or organs from a nonhuman animal source or human body, fluid, cells, tissues or organs that have ex vivo contact with live nonhuman animal cells, tissues or organs. It does not include the use of dead tissues.

Keywords: Cell, Organ, Tissue, Xenotransplantation

Introduction

Xenotransplantation is in contrast with allotransplantation (from other individual of same species), syngeneic transplantation or isotransplantation (grafts transplanted between two genetically identical individuals of the same species) and autotransplantation (from one part of the body to another in the same person).¹,²

History of xenotransplantation

The first attempt to use animal organs in humans was reported in the 1960s. James Hardy carried out the first human lung allotransplant in 1963. Reemtsma and colleagues tried transplantation of chimpanzee kidneys. The results were significant. One person survived for 9 months with normal kidney function before dying from immunosuppression, but some others had a rejection problem which was treated by steroid therapy. This incident proved that xenograft function is possible for a considerable period of time. Tom Starzl, who is one of the greatest pioneers in the field of kidney and liver allotransplantation, performed a handful of liver transplants between nonhuman primates and young patients in Colorado in the 1960s. In 1984 Baby Fae, an infant who received a baboon heart by Leonard Bailey and lived for 20 days and another is Jeff Getty; an AIDS patient who received a bone marrow transplant from a baboon in 1995, but rejected the transplanted marrow almost immediately. After this baboon to human heart, liver and kidney transplants were attempted, but none of these survived for more than 1 year. In 1997, biotransplant and Novartis introduced a technology of transplanting bone marrow from the donor to stimulate the recipient’s immune system to accept the donor organ as self-organ. A Swedish group headed by Carl Groth was the first to attempt pig islet transplantation in patients with diabetes in 1993.³,⁴

Uses

This technique is used for a wide range of conditions including replacement of the heart, lungs, liver and kidney. Xenotransplantation is also being developed for scenarios like diabetes, Cancer, neurodegenerative disorders, chronic pain control and ex
vivo perfusion events. Insulin producing islet cells from pigs into the pancreas of monkey with type-1 diabetes helped them to produce their own insulin in response to increase blood glucose levels. Also neural cells of pig can be used for refractory Parkinsonism. Patients with Huntingon’s disease which is a neurogenerative condition characterized by mental disturbances are receiving modified tissues from pigs as an experimental treatment. Xenotransplantation also is and has been a valuable tool used in research laboratories to study developmental biology.5-7

Animal sources for xenotransplantation

Selection of animal sources:

- Pigs are mostly preferred because they mature very quickly, produce large litters, have organs of comparable size and function to human organs in both infants and adulthood. They can also be bred in microbiologically controlled environment.
- As pigs are slaughtered for food, so there are less ethical objections.
- Pigs can be easily controlled for viral infections.
- Mostly pig organ and tissue are used due to same physiological and biochemical profile to that of humans. Also distant in evolutionary relationship.
- Monkeys on the other hand are undomesticated animals that cannot be kept in controlled environment. Hence it is difficult to raise them like that of pigs.
- There is little experience in breeding these animals. The cost of doing so is large and also they reproduce slowly. Finally their similarity to man possess ethical and moral problems. Like human, monkeys mature slowly and produce one offspring at a time.
- The genetic similarity between monkey and human could facilitate disease spread between donor and recipient.8-10

Problems in xenotransplantation

- There are ethical, social and economic problems regarding Xenotransplantation. The first one is rejection of the organ and cells in which the recipient’s body attacks the new organ and the other is the risk of introducing infection into human population. Besides this the cost is also uncertain. Cost includes rearing of specific pathogen free animals, laboratory tests for early diagnosis of infection, specialized staffs, monitoring and surveillance regimen.

A. Immunologic barrier

The different immunologic rejections are:

1. Delayed rejection.
2. Hyper acute rejection.
3. Cell based immune rejection.11

1. Hyper acute rejection (HAR)

It is characterized by immediate onset with hemorrhage, thrombosis and infiltration of neutrophils that leads to loss of function of the transplant. Here natural human antibodies attract and destroy the organs vasculature within minutes of exposure to human blood. The main target site of xenoreactive natural antibodies (XNA) is the gal epitope which is a non-reducing trisaccharide group, galactosyl alpha-(1, 3) -galactosyl β-1, 4-N-acetyl glucosamine. Man does not possess this epitope because of the absence of the enzyme that produces it. Higher primates recognize the gal epitope as non self and produce immune response to it. Human beings produce anti gal antibodies.

XNA produce their effect primarily through complement activation via natural killer cells (NK cells). The prevention of epitope can be achieved by producing knock out animals with disrupted alpha 1, 3 galactosyl transferase genes. It can be suppressed by expressing human complement modulating proteins such as hCD59 (protectin), human decay accelerating factor (DAF, Hcd55) and membrane cofactor protein (MCP, hCD46) in transgenic pigs. Hyper acute rejection is not a problem for non-vascular xenograft.12

2. Delayed xenograft or acute humoral xenograft (AHXR) rejection

This normally occurs within 24 hours of time. There is local activation of inflammatory cells leading to platelet coagulation and extravasations of leucocytes in blood capillaries of donor organs. Here host antibody and immune system binds to the vascular endothelium of the xenograft leading to its damage. The initial response is mediated by IgM. The presence of these xenograft natural antibodies alone leads to disseminated intravascular coagulation. This can be prevented by using thrombin inhibitor or bovine serum albumin conjugated to multiple gal molecules to destroy primate blood stream of the antigal antibodies.
3. Cell mediated rejection

It is based on cellular immunity and is mediated by natural killer cells and T-lymphocytes. Antigen presenting cells from the xenograft present peptides to recipient CD4+ T cells through MHC class 2 molecules, resulting in the production of interleukin. Rejection starts 1-2 weeks after transplantation. This can be prevented by the introduction of donor stem cells in the recipient’s bone marrow so that donor reactive T cells consider it as self.13,14

B. Physiological barriers

1. The body temperature of pig is 39°C, where as human body temperature is 37°C. So the functional activity of porcine enzymes at this lower temperature may be decreased.

2. Lifespan of a pig is 15 -16 yrs and nothing is known about the ageing in xenotransplanted organs. Also all porcine hormones may not be effective across the species barrier. For example porcine rennin does not cleave human angiotensin and porcine erythropoietin does not stimulate human erythropoiesis.

3. Same is the case in liver transplantation also. As liver is not only a toxifying and storage organ but also a source of many proteins such as albumin and clotting factors. Many of these are species specific and will function inadequately in human.14

Ethical issues

- Animal rights group strongly oppose killing animals to harvest their organs for human use.
- Due to religious sentiments people do not want genetically modified pig organs for life saving transplantation.
- The prohibition of consumption of pigs in Jewish and Islamic communities poses a great problem.

Advantages

1. It provides an unlimited source of organs. As approximately 10 people die each day waiting for organs to be available.
2. It allows for both advanced planning and timed harvesting of an organ for immediate transplantation.
3. Xenotransplant is a very good solution for irreversible organ failure.

Disadvantages

Xenozoonoses: This is the transmission of infectious agents between species via xenograft.

- Porcine endogenous retro virus (PERVs) is always a threat as it is integrated as provirus in the genome of all pigs, so they can infect human cells. Retro virus results in persistent infection and remains clinically quiescent for long periods before causing disease. so there should be an extensive screening and selection of donor animals with low expression of PERV to prevent PERV transmission.

- Other viruses carried by pigs are porcine herpes virus, rotavirus, parvo virus and circo virus.

- The transmission of human T cell lymphotrophic viruses (HTLV) and human immunodeficiency virus (HIV) from non human Primate to humans is possible due to presence of suitable receptor and similar metabolism in the infected cell.

- Coagulation dysfunction between recipient and donor along with inflammation contribute significantly to loss of the transplant.

- Human can be infected with monkey SV40 virus through polio and adeno virus vaccines made in monkey kidney cells. Some virus remain dormant in animals specially herpes virus and retro virus.

- Currently there are many exclusion criteria for donor swine that include the presence of human pathogens mostly mycobacterium tuberculosis and rabies, pathogens of immunocompromised human like Toxoplasma gondii and Salmonella spp.15

Prevention

- Breeding SPF animals and screening for specific pathogens markedly decreases the risk for transmission of diseases. Breeding of transgenic pigs can be done to overcome organ rejection Because these genetically altered pigs express specific human protein that make it difficult for human immune system to identify the porcine organ as foreign.

- A transgenic pig is bred by injecting a small amount of DNA similar to human gene sequence into a fertilized pig egg and then implanting that egg into a sow leading to pig’s birth.

- Xenotransplantation product will serve as vector for antibiotic resistant microbes. This can be
reduced by decreasing the use of antibiotics in herd.

- Elimination of all ruminant protein from the feed to prevent prion infection.
- Animal should be screened microbiologically for zoonoses and for other pathogens.
- Animals infected with certain pathogens should be excluded.
- The safety of public health factor is to be considered. If transplantation takes place, the recipient must undergo monitoring for the rest of his life time as there may be risk of acute infection.
- Animal to be used for graft procurement should be under close herd surveillance.\(^\text{16}\)

Funding: No funding sources
Conflict of interest: None declared

**References**